μM phosphate in 10 minutes at 30°. Inactivation was carried out by incubating solutions containing 0.25 mg. per ml. protein and 2×10^{-4} M NEM at room temperature, and diluting with a large excess of GSH at appropriate time intervals.

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Laboratory Preparation of Tetrakis-(hydroxymethyl)-phosphonium Chloride

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Tetrakis-(hydroxymethyl)-phosphonium chloride, $(HOCH_2)_4PCl$, which is made by treating phosphine with an aqueous solution of formaldehyde–hydrochloric acid, recently has attracted interest as an ingredient of certain resins which impart flame-resistance to cotton fabrics.[2a,b] The only available method for making this compound was reported by Hoffman in 1921.[3] His method is slow and somewhat hazardous, since frequent minor explosions occur during the reaction. Since it appeared that tetrakis-(hydroxymethyl)-phosphonium chloride, abbreviated THPC for convenience, would be in demand for laboratory and perhaps commercial use, improvements were required in the details of its preparation. The purpose of this report is to present a practical laboratory method for preparing THPC.

Heretofore, a temperature of 80° was considered most desirable and was used for treating phosphine with an aqueous solution of formaldehyde and hydrochloric acid.[3] At lower temperatures the reaction was thought to be slow and at higher temperatures the vapor pressure of the solution interfered with the absorption of phosphine. Since phosphine is spontaneously inflammable at 80°, frequent explosions occurred in the reaction vessel of the Hoffman method. By that method it required about 8 hours for the phosphine generated from 30 g. of aluminum phosphide to be absorbed and to react with 100 g. of formaldehyde–hydrochloric acid solution.

We have found that phosphine will react rapidly with formaldehyde–hydrochloric acid solutions at room temperature. Phosphine is more soluble in these solutions at 25° than at 80°, and at the lower temperature explosions are eliminated. If the reaction is carried out at 50°, explosions occur only occasionally. However, since heating is not necessary for the reaction, a temperature of about 25° is preferred; temperatures of 10 to 15° also are satisfactory. It appears that the primary factor which controls the amount of THPC that can be made in the laboratory from a specified amount of formaldehyde–hydrochloric acid solution in a given length of time is the amount of phosphine that can

(1) Deceased.

(2) (a) W. A. Reeves and J. D. Guthrie, U. S. Department of Agriculture, Agricultural and Industrial Chemistry Bulletin, AIC-364 (1953); (b) W. A. Reeves and J. D. Guthrie, Textile World, 104, 101 (1954).

(3) A. Hoffman, THIS JOURNAL, 43, 1684 (1921).

be made available. With two small laboratory generators, sufficient phosphine was made in 30 hours to make over 1100 g. of THPC. In this case the phosphine produced by 30 g. of aluminum phosphide was absorbed and allowed to react with 100 g. of formaldehyde–hydrochloric acid solution in less than one hour.

A good yield of THPC and an easily isolated product is obtained when about 4.2 moles of formaldehyde are used per mole of hydrochloric acid. Paraformaldehyde or polyoxymethylene may be substituted for the formaldehyde without affecting the rate of the reaction or yield of product.

The phosphine used may be made by any method desired. Relatively pure phosphine is obtained conveniently by treating aluminum phosphide with water at room temperature. This source supplies a steady stream of the gas. Aluminum phosphide is not generally available, but it can be made by igniting with adequate precautions a mixture of 1.5 to 2.0 parts (by weight) of powdered aluminum and one part of red phosphorus.

Experimental

A. Apparatus.—The apparatus consisted of two phosphine generators provided with safety water-seal pressure releases, and a reaction vessel. Each generator consisted of a two-liter filter flask fitted with a two-hole rubber stopper. Through one of the holes was an inlet tube used to admit nitrogen and the other was connected to a safety water-seal pressure release. The water-seal pressure release could be of any convenient design as long as the water levels in it can be varied from 0 to about 15 inches. The side arm of each filter flask was connected to the reaction vessel. The reaction vessel was a five-liter jar fitted with a four-hole wooden cover. The inlet tubes, which consisted of gas dispersion filter tubes, passed through two of the holes and extended nearly to the bottom of the vessel. A high speed stirrer and a vent tube were mounted through the other two holes.

B. Reagents.—(1) Nitrogen. (2) Formaldehyde–hydrochloric acid solution was prepared by mixing 37% formaldehyde and 35% hydrochloric acid so that the final solution contained these reagents in about a 4.2:1 mole ratio, respectively. (3) Aluminum phosphide: about 100-g. portions of a mixture of 528 g. of powdered aluminum and 352 g. of red phosphorus were placed on an asbestos mat in a fume hood and ignited with a match. The combined portions made about 880 g. of crude aluminum phosphide. Small portions of the aluminum–phosphorus mixture were ignited because intense heat and toxic vapors are produced when these reagents are burned. (4) Phosphine was generated by adding aluminum phosphide to water in the apparatus described above.

C. Procedure.—All operations were performed in a well ventilated hood because of the toxicity of phosphine. About 1600 ml. of water was added to each phosphine generator, then water was added to each safety water-seal pressure release tube. Formaldehyde–hydrochloric acid solution, made by combining 660 g. of 35% aqueous hydrochloric acid and 2100 g. of 37% aqueous formaldehyde, was put into the reaction vessel. The stirrer in the reaction vessel was adjusted for vigorous agitation and then the apparatus was swept out with nitrogen by allowing a steady stream of the nitrogen to pass through it for about 10 minutes. At the time the nitrogen was stopped, about 5 g. of aluminum phosphide was added to each generator. After about one hour, 15 g. of aluminum phosphide was added to each generator and so on at hourly intervals until the 880 g. had been added. Two hours after the last addition of aluminum phosphide the reaction vessel was disconnected and the solution was transferred to large evaporating dishes. The volatile components were evaporated at about 70 to 75° with stirring until crystals began to form, when the mass was transferred to a desiccator and allowed to cool to room temperature over sodium hydroxide pellets. The entire mass crystallized. Approximately 1135 g. of 95% THPC

was obtained, a yield of about 90% based on the amount of formaldehyde and hydrochloric acid used. The crude THPC melted at about 145°. The pure compound, which melts at 151°, can be obtained by recrystallizing from acetic acid.[3]

At about 25°, the absorption of phosphine and its reaction with formaldehyde and hydrochloric acid are rapid until about 85 to 90% of these materials are converted to THPC. In order to avoid the escape of unused phosphine, which is likely to occur near the end of the reaction, the reaction should be discontinued when an amount of THPC has been made that is equivalent to about 85 to 90% of the formaldehyde originally present in the solution. This endpoint can be determined conveniently by removing a small sample of the solution, evaporating the volatile components and weighing the crystalline THPC. The maximum temperature at which the evaporation can be carried out and still obtain crystals is not known, but when the solution is evaporated on a hot-plate at relatively high temperatures, a viscous sirup is obtained which is difficult, if not impossible, to crystallize. The sirup is probably a mixture of THPC and tris-(hydroxymethyl)-phosphine oxide since it is known that phosphonium compounds are converted to phosphine oxides by heat.

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(4) One of the laboratories of the Southern Utilization Research Branch, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

Some Halophenoxyacetic Anhydrides

BY GEORGE SVARNAS AND WILLIAM L. HOWARD

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Interest in the herbicidal properties of 2,4-dichlorophenoxyacetic acid and related compounds[1] suggested that the preparation of the anhydrides of some phenoxyacetic acids might prove useful. Accordingly, three representative anhydrides have been prepared: 2,4-dichlorophenoxyacetic anhydride, 4-fluorophenoxyacetic anhydride and 2,4-difluorophenoxyacetic anhydride. Thompson, et al.,[2] have reported 2,4-dichlorophenoxyacetic anhydride, but, since no details are given, its preparation is presented herewith. 4-Fluorophenoxyacetyl chloride and 2,4-difluorophenoxyacetyl chloride, prepared as intermediates, and the corresponding amides have not been reported previously.

Qualitative observations during the preparation of these compounds indicated that the acid chlorides and anhydrides are intermediate in reactivity between the corresponding derivatives of the typical aromatic and aliphatic acids. Because of their

(1) M. E. Synerholm and P. W. Zimmerman, Contrib. Boyce Thompson Inst., 14, 91 (1945); R.L. Weintraub, J. Agr. Food Chem., 1, 250 (1953).
(2) H. E. Thompson, C. P. Swanson and A. G. Norman, Botan. Gaz., 107, 476 (1946).

sensitivity to hydrolysis, moisture was carefully excluded throughout the preparations.

It is of interest to note that phenoxyacetic acid melts at a considerably higher temperature than its anhydride. The anhydrides reported here exhibit the same relationship.

All pertinent data concerning the compounds prepared are listed in Table I. The melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected.

Experimental

Preparation of the Acid Chlorides.—The acid[3] is refluxed with about two equivalents of thionyl chloride for 2–3 hours. After the excess thionyl chloride has been removed at the aspirator the residual liquid is vacuum distilled.

Preparation of the Amides.—A benzene solution of the acid chloride is added portionwise with stirring to a flask containing benzene into which dry ammonia is being passed, an excess of ammonia being maintained during the entire addition. After being allowed to stand overnight the mixture is filtered and the solid is washed thoroughly with water. Concentration of the benzene filtrate yields more product, after which the crops are combined and recrystallized from benzene or acetone–benzene.

Preparation of the Anhydrides.—The silver salt of the phenoxyacetic acid is prepared by converting the acid to the sodium salt with the equivalent amount of aqueous sodium hydroxide, after which the equivalent amount of aqueous silver nitrate is added to the hot solution with vigorous stirring. The precipitated silver salt is filtered off without delay, washed successively with water, ethanol, and ether, and then dried in vacuo.

Slightly more than one mole of the freshly prepared, finely divided silver salt is refluxed with a mole of the acid chloride in ligroin (d. 0.72–0.74) for one to three days. The hot supernatant liquid then is decanted into a flask, the flask is stoppered, and the solution is allowed to cool to room temperature during which time an oil separates and eventually solidifies. The solid product is then recrystallized from benzene–ligroin.

TABLE I

Compound	M.p. or b.p. (mm.), °C.	Carbon, % Calcd.	Carbon, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Yield, %
4-FC₆H₄OCH₂COCl	106–107 (9)	50.94	50.80	....	....	3.21	3.06	73.3
2,4-F₂C₆H₃OCH₂COCl	96 (7)	46.51	46.51	....	....	2.44	2.57	69.0
4-FC₆H₄OCH₂CONH₂	109.5–110.5	...	...	8.29	8.35	..	..	75.5
2,4-F₂C₆H₃OCH₂CONH₂	123.5–125	...	...	7.49	7.55	..	..	83.0
(4-FC₆H₄OCH₂CO)₂O	54.5–56	59.63	59.86	161[a]	159[a]	3.75	3.93	47.5
(2,4-F₂C₆H₃OCH₂CO)₂O	73.5–74.5	53.66	53.69	179[a]	177[a]	2.81	2.97	75.0
(2,4-Cl₂C₆H₃OCH₂CO)₂O	76.5–77.5	45.32	45.52	212[a]	212[a]	2.38	2.31	42.5

[a] Saponification equivalent.

(3) The fluorophenoxyacetic acids were prepared from the corresponding phenols obtained from the Illinois State Geological Survey. The 2,4-dichlorophenoxyacetic acid was obtained from the Eastman Kodak Co.

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Rates of Aminolysis

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Table I records first-order rate constants for the solvolysis of seven compounds in various amine solutions. The results are striking from the point of view of the Brönsted catalysis law for bases. The ratio of rate constants for n-butylamine and aniline

(1) National Science Foundation Fellow, 1952–1953. For further experimental data see D. C. Dittmer, Ph.D. thesis, M.I.T., September, 1953.